PATENT COOPERATION TREATY

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	14.02.2001
Applicant's or agent's file reference 1038-985 MIS	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00938	07/10/1999	07/10/1998

Applicant
CONNAUGHT LABORATORIES LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Emslander, S Tel.+49 89 2399-8718

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1038-985 MIS		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00938	07/10/1999	07/10/1998
International Patent Classification (IPC) or national classification and IPC C12N15/70		
Applicant CONNAUGHT LABORATORIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/05/2000	14.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Armandola, E Telephone No. +49 89 2399 7493

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00938

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-64 as originally filed

Claims, No.:

1-36 as originally filed

Drawings, sheets:

1/81-81/81 as originally filed

Sequence listing part of the description, pages:

1-128, filed with the letter of 17.02.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 12 and 25 (partially) for N, IS, IA; 30 and 31 for IA .

because:

   ☒ the said international application, or the said claims Nos. 30 and 31 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 12 and 25 (partially).

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. all claims except for those parts of claims 12 and 25 for which an ISR was not established (some of the sequences).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17, 19-36
	No:	Claims	18
Inventive step (IS)	Yes:	Claims	1-11, 13-17, 19-36
	No:	Claims	12, 18
Industrial applicability (IA)	Yes:	Claims	1-29, 32-36
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Novelty, inventive step and Industrial applicability (Art. 33 (2), (3), (4) PCT)

Claims 12 and 25

The international preliminary examination is being carried out only on the part of Claims 12 and 25 referring to the first three inventions as defined in the ISR. The part of Claims 12 and 25 referring to remaining inventions (SEQ. ID. NO: 33-35, 38, 39, 42, 43, 46, 47, 50, 51, 54, 55, 58, 59, 62 and 63) will not be examined due to the non-establishment of an international search report for these parts of the claims see also ISR).

Industrial Applicability (Art 33 (4) PCT)

Claims 30 and 31 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

For the assessment of the present Claims 30 and 31, with regard to methods of treatment of the human body, on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV

Lack of unity of invention

The IPEA agrees with the objection made by the International Search Authority about the lack of unity of the present application in view of Rule 13 PCT.
The following inventions have been identified:

1. Claims 1-11, 13-16 and 32-36 (completely); 18-20 and 25-31 (partially):
A nucleic acid molecule comprising a promoter functional in *E. coli* and operatively linked to a modified operon of a non-typeable strain of *Haemophylus* comprising A, B, C genes, wherein the A gene contains a nucleic acid sequence which codes for a mature high molecular weight protein of the non-typeable strain of *Haemophylus*. Use in immunogenic compositions and vaccine formulations.

2. Claims 18-20 (partially):
A plasmid vector for the expression of a high molecular weight protein of a high molecular weight protein of a non-typeable strain of *Haemophylus* and comprising a T7 promoter, a cloning site for the insertion of a nucleic acid molecule into the plasmid and the portion B and C of the operon of a non-typeable *Haemophylus* strain.

3. Claims 12, 17 and 21-31 (partially):
An isolated and purified nucleic acid molecule encoding a high molecular wight protein of a non-typeable *H. influenzae* strain; a corresponding isolated, immunologically protective protein; corresponding immunogenic compositions and vaccine formulations, wherein the strain of *H. influenzae* is Joyc (SEQ. ID. NO: 25-32).

4. Claims 12, 17 and 21-31 (partially):
The same as 3., limited to strain K21 (SEQ. ID. NO: 33-41).

5. Claims 12, 17 and 21-31 (partially):
The same as 3., limited to strain LCC2 (SEQ. ID. NO: 42-49).

6. Claims 12, 17 and 21-31 (partially):
The same as 3., limited to strain PMH1 (SEQ. ID. NO: 50-57).

7. Claims 12, 17 and 21-31 (partially):
The same as 3., limited to strain PMH15 (SEQ. ID. NO: 58-65).

The 7 inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

High molecular weight gene operons HMW1ABC and HMW2ABC from non-typeable strains of *Haemophylus* were known in the prior art. Vectors for the recombinant expression of these genes have been described (see ISR, e.g. WO97/36914, Barenkamp et al. 1994, WO94/21290), as well as immunogenic compositions comprising HMW1 and HMW2.

In the light of the prior art, the problem to be solved by the present application can be seen as the provision of gene operons and of isolated nucleotide sequences encoding the HMW1 and HMW2 protein from additional non-typeable strains of *Haemophylus*, vectors to express HMW proteins and methods to purify them, as well as immunogenic compositions containing the HMW1A and HMW2A proteins from these strains and methods to induce protection against diseases caused by *Haemophylus*.
The solution is provided with the gene operons HMW1ABC and HMW2ABC, the DNA sequences encoding the HMW1 and HMW2 proteins from several non typeable strains of *Haemophylus* and a vector capable of expressing HMW proteins in general.
The seven inventions are linked by their relation to the HMW protein family of *Haemophylus;* this family as well as genes and proteins belonging to it were, however, known.

No other special technical feature (in the sense of Rule 13.2 PCT) can be identified linking the inventions that can be regarded as a single inventive concept (Rule 13.1 PCT).

As the applicant has paid the required additional examination fees, the examination will be performed on all 7 inventions as identified above except for those parts of inventions 4-7 in Claims 12 and 25 for which no IRS was provided (SEQ. ID. NO: 33-35, 38, 39, 42, 43, 46, 47, 50, 51, 54, 55, 58, 59, 62 and 63) (see ISR, Box II).
The ISR has been provided for the first three inventions. It is the opinion of this authority that the search performed for the first three inventions would have retrieved relevant prior art for the other four inventions as well, excluding the specific sequences claimed in Claims 12 and 25 and for which no sequence similarity search was performed. For this reason, no opinion will be expressed on the novelty, inventive step and industrial applicability of these sequences.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 97 36914 A (BARENKAMP STEPHEN J) 9 October 1997 (1997-10-09) cited in the application

D2: BARENKAMP S J ET AL: 'GENES ENCODING HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS OF NONTYPEABLE HAEMOPHILUS INFLUENZAE ARE PART OF GENE CLUSTERS' INFECTION AND IMMUNITY,US,AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, vol. 62, no. 8, 1 August 1994 (1994-08-01), pages 3320-3328, XP000578342 ISSN: 0019-9567 cited in the application

D3: WO 94 21290 A (BARENKAMP STEPHEN J ;ST GEME JOSEPH WILLIAM III (US)) 29 September 1994 (1994-09-29)

D4: ST. GEME III, J.W. ET AL.: 'Secretion of the Haemophilus influenzae HMW1 and HMW2 adhesins involves a periplasmic intermediate and requires the HMWB and HMWC proteins.' MOL. MICROBIOL., vol. 27, no. 3, February 1998 (1998-02), pages 617-630, XP000892544 cited in the application

Novelty and Inventive step (Art.33 (2), (3) PCT)

1. Claim 18 cannot be considered novel because documents D1-D4 disclose vectors (e.g. pHMW1-15 and pHMW2-21) which fall under the scope of the claim, namely they can be used for the expression of a HMW protein of a non typeable strain of *H. influenzae*, contain the T7 promoter, cloning sites for the insertion of a nucleic acid molecule and the B and C portions of the HMW operon. The wording used in the claim, in particular the word "comprising", does not limit sufficiently the scope of the claim so that it can clearly be distinguished from the prior art. Both plasmids containing only the portions B and C of the operon plasmids containing portions A, B and C of the operon, fall under the definition "a plasmid comprising the portions B and C of the operon". The word "comprising" does not exclude that other parts of the operon or other structural features might be present in the plasmid.

2. Claim 12 cannot be considered to entail an inventive step for the following reasons:
D1-D4 disclose isolated nucleic acids encoding HMW proteins from *H. influeanzae.*
The difference between the disclosure of D1-D4 and the subject-matter of the claim resides in the different strain of origin of the nucleic acids claimed.
The problem to be solved can, therefore, be seen as the provision of additional HMW-encoding nucleic acids derived from various strains of *Haemophylus.*
The skilled person would not have needed to exercise inventive skills to solve this problem by using standard techniques normally employed to isolate homologous genes from different bacterial strains.
It should be noted that the provision of additional sequences, as alternatives to a known sequence, even if derived from different strains of an organism, without the identification of special or unexpected technical features or properties which characterize them, cannot be considered to entail an inventive step.

3. Claims 1-11, 13-17 and 19-36 can be considered novel and inventive as the nucleic acid and proteins, compositions and methods to induce protective immunity to *H. influenzae* described in the claims have not been described in the prior art.
The prior art describes the production of recombinant HMW1 and HMW2 proteins by using expression vectors containing the complete HMW operons (see e.g. D1 and D3); the proteins so produced have not been demonstrated to have a protective effect on immunized subjects. Only complexes of HMW1 and HMW2 proteins have been shown in the prior art to have a protective effect. The modifications of the A gene (truncation of 5' sequences) described in the application are not disclosed.
From the available prior art the skilled person would have had no hints as to how to solve the problem of efficiently producing recombinant uncomplexed HMW proteins which can be effectively used for immunization.
The claims are, therefore, considered inventive.